PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	10 May 2005 (10-05-2005)
Applicant's or agent's file reference 29399-0077	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA2004/002196	23 December 2004 (23-12-2004)	23 December 2003 (23-12-2003)

International Patent Classification (IPC) or both national classification and IPC[7]
A61K 31/675

Applicant
MEDICURE INTERNATIONAL INC. ET AL

1. This opinion contains indications relating to the following items :

[X]	Box No. I	Basis of the opinion
[X]	Box No. II	Priority
[X]	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
[X]	Box No. IV	Lack of unity of invention
[X]	Box No. V	Reasoned statement under Rule 43*bis*.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement.
[ ]	Box No. VI	Certain documents cited
[X]	Box No. VII	Certain defects in the international application
[X]	Box No. VIII	Certain observations on the international application

2. **FURTHER ACTION**
If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001(819)953-2476	Authorized officer Stephanie Michaud (819) 934-2328

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] This opinion has been established on the basis of a translation from the original language into the following language ,which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of :

   a. type of material

      [ ] a sequence listing

      [ ] table(s) related to the sequence listing

   b. format of material

      [ ] in written format

      [ ] in computer readable form

   c. time of filing/furnishing

      [ ] contained in the international application as filed.

      [ ] filed together with the international application in computer readable form.

      [ ] furnished subsequently to this Authority for the purposes of search.

3. [ ] In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statement that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments :

Box No. II Priority

1 [ ] The following document has not yet been furnished :

[ ] copy of the earlier application whose priority has been claimed (Rule 43bis.1 and 66.7(a)).

[ ] translation of the earlier application whose priority has been claimed (rule 43bis.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2 [ ] This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purpose of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary :

The priority document pertaining to the present application has not been verified at the time of establishing this first written opinion. Hence, it is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is incorrect, the WO 04/006919 application cited in the international search report could become relevant in assessing whether claims 1-4, 8-17, 19-20, 25-27, 31-37 meet the criteria set forth in Article 33 (2-4) PCT.

Box No. III **Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of :

[ ] the entire international application

[X] claim Nos. 1-37 (part)

because:

[X] the said international application, or the said claim Nos. 8-37
relate to the following subject matter which does not require an international preliminary examination *(specify)* :

The subject matter of claims 8-37 relates to a method of medical treatment of the human or animal body. (Rule 39.1 (iv) PCT) For the assessment of these claims on the question whether they are industrially applicable, no unified criteria exists in the PCT. The patentability can also be dependent upon the formulation of the claims. Certain national offices do accept claims worded as method of medical treatment while others rather accept claims worded as use claims and would then recognize an industrial applicability for these claims. Under the PCT Rules, no industrial applicability can be acknowledged.

[X] the description, claims or drawings *(indicate particular elements below)* or said claim Nos. 1-37 (part)
are so unclear that no meaningful opinion could be formed *(specify)* :

See Supplemental Box for further details.

[ ] the claims, or said claims Nos. are so inadequately supported
by the description that no meaningful opinion could be formed.

[ ] no international search report has been established for said claims Nos.

[ ] the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that :

the written form [ ] has not been furnished

[ ] does not comply with the standard

the computer readable form [ ] has not been furnished

[ ] does not comply with the standard

[ ] the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

[X] See Supplemental Box for further details.

Box No. IV **Lack of unity of invention**

1. [ ] In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has :

   [ ] paid additional fees

   [ ] paid additional fees under protest

   [ ] not paid additional fees

2. [X] This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   [ ] complied with

   [X] not complied with for the following reasons :

   Group A: Claims 1-18 are directed to a pharmaceutical composition comprising a HMG CoA reductase inhibitor and a vitamin B6 related compound and methods of use therein.

   Group B: Claims 19-37 are directed to a method of treating or preventing hypercholesterolemia and a method of treating a patient at risk of cardiovascular disease, said patient at risk of cardiovascular disease already taking a HMG CoA reductase inhibitor, comprising administering a therapeutically effective dose of a vitamin B6 related compound.

4. Consequently, this opinion has been established in respect of the following parts of the international application :

   [ ] all parts

   [X] the parts relating to claim Nos. 1-37 (part)

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-37 (part)	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-37 (part)	NO
Industrial applicability (IA)	Claims	1-7 (part)	YES
	Claims		NO

2. Citations and explanations :

D1: Canadian Journal of Cardiology, 1995, Vol. 11 (Supp C), pages 18C-23C, FROHLICH
D2: WO 00/57863 (DHALLA), 5 October 2000, (2000-10-05)
D3: WO 00/53606 (HAQUE), 14 September 2000, (2000-09-14)
D4: WO 01/64692 (HAQUE), 7 September 2001, (2001-09-14)
D5: Lipids in Health and Disease, 18 September 2003, Vol 2(7), DUMM et al.
D6: US 5288716 (SPECK), 22 February 1994, (1994-02-22)
D7: Journal of Lipid Research, 1 September 2003, (2003-09-01), Vol. 44, pages 2019-2029, CHAUHAN
D8: Injury Prevention, 2002, Vol. 8, pages 276-279, RAY et al.
D9: WO 97/38694 (TOBERT), 23 October 1997, (1997-11-23)

Document D1 discloses that lipoprotein(a) and homocysteine are the main risk factors in coronary heart disease. The risk due to Lp(a) can be lowered by decreasing the patients' LDL cholesterol with statins (HMG CoA reductase inhibitors) and the treatment of increased homocysteine is accomplished with folic acid administration or vitamin B6.

Document D2 discloses pyridoxal-5'-phosphate, pyridoxal and pyridoxamine as useful in treating cardiovascular related diseases and conditions.

Document D3 discloses the 3-acylated analogue of pyridoxal and 3-acylated analogue of pyridoxal-4,5-aminal as useful in treating cardiovascular and related diseases.

Document D4 discloses the pyridoxine phosphate analogue as useful in treating cardiovascular and related diseases, and diabetes mellitus and related diseases.

Document D5 discloses that pyridoxine supplementation induced a significant increase in total plasma homocysteine level and also a lowering effect in plasma total cholesterol and triglycerides.

Document D6 discloses pyridoxine derivatives, more particularly pyridoxal, pyridoxamine and precursors and their metabolites prevent and treat hyperlipidemia and atherosclerosis.

Document D7 discloses that the clinical use of statins to reduce endogenous synthesis of cholesterol might reduce the progression of AD.

Document D8 discloses the clinical use of statins and lipid lowering agents in reducing osteoporotic fractures.

Document D9 discloses combination therapies for reducing the risks associated with cardiovascular disease comprising the administration of a therapeutically effective amount of an HMG CoA reductase inhibitor in combination with the B vitamin, folic acid.

See Supplemental Box

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted :

The description does not comply with PCT Article 5 since page 11, line 5 of the description incorrectly references US Patent No. 6,585,414 that relates to a Container with Swinging Partition. It is believed that US Patent No. 6,586,414 may have been intended in lieu of 6,585,414.

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made :

Claim 1, 24 do not meet the requirements of PCT Article 6 because the subject-matter is defined in terms of the result to be achieved rather than in terms of technical features, as required by PCT Rule 6.3(a). The following expressions are considered to be functional features: "HMG CoA reductase inhibitor" and "vitamin B6 related compound".

The terms "3-acylated analogue of pyridoxal"; "3-acylated analogue of pyridoxal-4,5-aminal", and "pyridoxine phosphate analogue" relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found for only a very small proportion of compounds possible in claims 3, 19, 26.

Claim 16 is ambiguous within the meaning of PCT Article 6. There appears to be missing words in the claim.

Reference to the pharmaceutical composition according to claim 16 in claim 23 causes a lack of clarity within the meaning of PCT Article 6 since the claim preamble of independent claim 16 is directed to a method.

The negative limitation on the meaning of "vitamin B6 related compound" described at page 16, line 24 - page 17, line 2 causes a lack of clarity within the meaning of PCT Article 6. If the negative limitation is intended to be applied to the claimed subject matter, it must be explicitly defined within the claims.

A statement in an application, such as found on page 11, lines 6-7 which incorporates by reference any other document, does not comply with PCT Article 5.

The paragraph of page 19, lines 10-14 of the description does not comply with PCT Article 6, because it implies that the protection sought goes beyond the scope of the claims.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box No. III

Claims 1, 2-23 (part), 24, 25-37 (part):

Claims 1, 24 do not meet the requirements of Article 6 PCT because the subject-matter is defined in terms of the result to be achieved rather than in terms of technical features, as required by Rule 6.3(a) PCT. Thus, the following expressions are considered to be functional features:

"HMG CoA reductase inhibitor"; and "vitamin B6 related compound".

Since the components of the pharmaceutical composition of claim 1 and use thereof in the method of claim 24 are defined solely by reference to desirable characteristics, namely as "HMG CoA reductase inhibitor" and "vitamin B6 related compound" a meaningful search over the whole of the claimed scope within the meaning of Article 6 PCT for claims 1, 24 is impossible. Furthermore, the use of the expression "analogue" (claim 3) in the present context is also considered to lead to a lack of clarity within the meaning of Article 6. The lack of clarity with respect to the functional claiming and ambiguous definitions is such as to render a meaningful and complete search impossible. Due to the multiple meanings that can be arrived at for "HMG CoA reductase inhibitor"; "vitamin B6 related compound"; "3-acylated analogue of pyridoxal"; "3-acylated analogue of pyridoxal-4,5-aminal", and "pyridoxine phosphate analogue", a complete prior art search was precluded and limited to those components of the composition that appear to be supported. Therefore, the search was limited to those pharmaceutical compositions and method of use therein comprising the HMG CoA reductase inhibitors defined in claim 2, and the vitamin B6 related compounds: pyridoxal, pyridoxal-5'-phosphate, or pyridoxamine of claim 3, the 3-acylated analogues of pyridoxal defined in claim 5, the 3-acylated analogues of pyridoxal-4,5-aminal defined in claim 6, and the pyridoxine phosphate analogues defined in claim 7, for the pharmaceutical compositions and method of use therein defined in claims 2-23 (part), 25-37 (part).

Continuation of Box No. V:

Novelty

Group A: Claims 1-18 (part)

The subject-matter of claims 1-18 is novel vis-à-vis D9, due to the inclusion of vitamin B6 related compounds as *lipid* lowering agent in lieu of folic acid that is defined as a *homocysteine* lowering agent, to the pharmaceutical composition comprising a HMG CoA reductase inhibitor. Additionally, the methods for treating the diseases defined in claims 16-18 are also not disclosed. The subject-matter of claims 1-18 is not disclosed in the prior art and therefore satisfies the requirements of Article 33(2).

Group B: Claims 19-37 (part)

The subject-matter of claims 19-37 is novel vis-à-vis D5 and D6, due to the use of vitamin B6 related compounds defined as 3-acylated analogue of pyridoxal; 3-acylated analogue of pyridoxal-4,5-aminal, and pyridoxine phosphate analogue, as lipid lowering agent in lieu of vitamin B6 (D5) or pyridoxal, pyridoxamine and precursors and their metabolites (D6). The subject-matter of claims 19-37 is not disclosed in the prior art and therefore satisfies the requirements of Article 33(2).

(Continued on next page)

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box No. V

Inventive Step

Group A: Claims 1-18 (part)

Statins (HMG CoA reductase inhibitors) are currently one of the most used lipid lowering drugs not only for cardiovascular health but also for other diseases such as diabetes, osteoporosis and Alzheimer's disease. See for instance D1, D4, D7-D9. That vitamin B6 and the vitamin B6 related compounds of the alleged invention are useful in cardiovascular disease is known from D2 to D4. The therapeutic activity of vitamin B6 and the vitamin B6 related compounds of the alleged invention in treating cardiovascular and related disease taught in D2 to D4 is attributed to raised PLP levels (pyridoxal-5'-phosphate), the biologically active form of vitamin B6 inside cells and in blood plasma, by the *in vivo* metabolism of said vitamin B6 and vitamin B6 related compounds. Vitamin B6 and vitamin B6 related compounds are therefore considered equivalent since all (with the exception of "pyridoxine phosphate analogue") will yield the same end result, increased PLP *in vivo* (the "pyridoxine phosphate analogue"will yield a PLP analogue with similar activity to PLP (D4)) for benefit in treating cardiovascular disease. D1 discusses the risk factors of raised lipoprotein and raised homocysteine together and suggests that a suitable treatment regime is the administration of vitamin B6 for lowering the homocysteine levels and a statin for lowering both serum LDL levels and serum triglycerides. The applicant has attempted to overcome this known combination of a HMG CoA reductase inhibitor and vitamin B6 by stating that the utility of the vitamin B6 or vitamin B6 related compounds in the composition with a HMG CoA reductase inhibitor of the alleged invention lies its ability to act as a lipid-lowering agent only and not as a homocysteine reducing agent (description *vide supra* page 3). However, the lipid lowering ability of vitamin B6 and its derivatives therein is known in the art. D5 teaches that vitamin B6 reduces both homocysteine levels and plasma total cholesterol and D6 teaches that administration of compounds of the alleged invention, such as pyridoxal and pyridoxamine, results in a marked reduction in serum lipids, particularly LDL cholesterol and also notes a lack of toxic effect on the liver. Since the combination of vitamin B6 and a HMG CoA reductase inhibitor in treating cardiovascular and related disease is known from D1, and both D5 and D6 teach that vitamin B6 and derivatives therein are known lipid-lowering agent, further defining the utility of the vitamin B6 and vitamin B6 related compounds as lipid lowering agents in the alleged invention does not render the claimed subject matter inventive. Claims 1-18 do not satisfy the criteria set forth in Article 33(3) PCT because the subject-matter does not involve an inventive step (Rule 65(1)(2) PCT).

Group B: Claims 19-37(part)

The use of vitamin B6 and derivatives therein to reduce plasma total cholesterol is known from D5 and D6. From the teachings of D2 to D4, the therapeutic activity of vitamin B6 and the vitamin B6 related compounds of the alleged invention in treating cardiovascular and related disease taught in D2 to D4 is attributed to raised PLP levels (pyridoxal-5'-phosphate), the biologically active form of vitamin B6 inside cells and in blood plasma, by the *in vivo* metabolism of said vitamin B6 and vitamin B6 related compounds. Vitamin B6 and vitamin B6 related compounds are therefore considered equivalent since all (with the exception of "pyridoxine phosphate analogue") will yield the same end result, increased PLP *in vivo* (the "pyridoxine phosphate analogue"will yield a PLP analogue with similar activity to PLP (D4)) for benefit in treating cardiovascular disease. Since the use of vitamin B6 and derivatives therein in lowering plasma cholesterol is known in the art (D5, D6) and the vitamin B6 related compounds act in the same manner as vitamin B6, their use is considered equivalent. The person skilled in the art would have applied the compounds of the "vitamin B6 related compounds" of the alleged invention and expected the same result. Absent from any demonstration of improvement or unexpected results having been imparted to the claimed invention, the use is considered equal to or obvious over the teachings of D6 in view of D2 to D4. The present application does not satisfy the criteria set forth in Article 33(3) PCT because the subject-matter of claims 19-37 does not involve an inventive step.

Industrial Applicability

The subject matter of claims 1-7(part) is considered to be industrially applicable and thus fulfilling the requirements of Article 33(4) PCT. For the assessment of claims 8-37 (part) on the question of industrial applicability, no unified criteria exists in the PCT. The Canadian Intellectual Property Office, for example does not allow claims directed towards methods of medical treatment but may allow claims directed to the use of a known compound for a new medical treatment as well as to the use of a new compound for a medical treatment.